Asian Pacific Journal of Environment and Cancer
Vol 4 No 1 (2021), 39-43
Original Research

Monitoring Therapeutic Side Effects (carcinogenic and non-carcinogenic) with Linked Cancer Registry Data in Australia

David Roder
Cancer Epidemiology and Population Health, Allied Health & Human Performance, University of South Australia, South Australia, Australia.

Elizabeth Buckley
Cancer Epidemiology and Population Health, Allied Health & Human Performance, University of South Australia, South Australia, Australia.

Population-based cancer registries (PBCRs) continue to have a crucial role in surveillance of cancer incidence, mortality, survival and prevalence in different countries. The International Agency for Research on Cancer has used PBCR data as its principal touchstone for estimating cancer and cancer mortality risk worldwide and by country. PBCRs have provided evidence for service planning, evaluation, and quality improvement, and population health and health system research. Increasingly they are being used as a spine for linking data from other databases relating to primary prevention initiatives, screening, treatment provision, and the delivery of support services. PBCRs have long been used in investigations of environmental hazards, as applying for example to exposures to radon, asbestos dust, and agricultural chemicals. The required data for these investigations are generally not available from PBCRs as a one-stop data source, but from PBCRs supplemented with data on exposures collected through surveys, industry records, and increasingly, from linked databases. Cancer survival has increased markedly in economically developed countries in through advances in surgery, radiotherapy, and systemic therapies. The net gains have often been impressive but adverse effects are occurring. New chemotherapy and other systemic therapies can be associated with carcinogenesis and other adverse effects on cardiac and other vital organs. These effects may not be detected until extensive latency periods have passed. An important role of linked datasets is to flag possible adverse effects, their potential scale, and population distribution, and to indicate where further research is warranted. This report discusses the use of PBCRs in monitoring carcinogenic and noncarcinogenic side effects, and the role of data linkage as an enabler. The opportunities to use PBCRs for this purpose depend on their availability, access to relevant disease registries, administrative data, and death data. Opportunities would also vary depending on competing priorities and availability of an enabling legal framework.

Introduction

Opportunity exists in Australia to use linked data across registries and administrative databases to investigate and monitor the health of cancer patients long after their initial treatment [1, 2]. This infrastructure can also be used to monitor quality and technical appropriateness of care and gains in survival from therapeutic advances [3-6]. With linkage to census and welfare data, capacity is increased to identify sociodemographic disparities and determine whether gains are being made in reducing disparities across sub-groups at special risk [7].

Another potential application of linked data infrastructure is monitoring outcomes of cancer care, including side effects from new pharmaceutics and radiation oncology treatments [8, 9]. This capacity is enhanced in Australian jurisdictions where cancer registry linkages include data from screening and vaccination registries, hospital inpatient and emergency departments, radiotherapy centres, universal health insurance claims and death records [1, 2]. This breadth of data linkage is quite new in Australia. We anticipate that linked data will be important for health surveillance and monitoring of health-care outcomes in an environment of rapidly evolving therapies [10].

Australia already collects data on adverse medical events, including serious reactions to medications, through the Australian Advisory Committee on Medicines [11]. The Government's Quality Use of Medicines program has long been responsible for using these data to minimize preventable adverse effects. Despite the value of these data, suboptimal reporting exists due to reliance on voluntary reporting and discretionary interpretation by practitioners as to which medical events qualify for reporting [11].

There is proof of concept of the value of cancer registries for investigating chemical and radiation exposures of non-medical origin in Australia and elsewhere [12-14]. We consider unrealized opportunities exist to use cancer registries and linked data as a health surveillance tool for detecting and investigating medical exposures. Evidence of the global burden of side-effects from pharmaceutical exposures, particularly long-term side-effects, is limited by data availability. Better evidence of trade-offs of benefits and harms are required, particularly for novel therapeutic drugs, to better inform treatment regulations and policies, and treatment selection for individual patients. Adverse effects may include carcinogenic effects of the medical therapeutic environment, including from radiation exposure and pharmaceutics, or non-carcinogenic effects such as adverse effects on heart health or the functioning of kidneys and other organs [9, 15]. Enhancements to linked cancer-registry infrastructure offer important opportunities to detect and monitor these effects.

The use of cancer registries to identify non-medical correlates of cancer risk is already well-established [12-14, 16, 17]. The emerging infra-structures of cancer registries linked with other health databases are discussed now, along with the potential to use this infra-structure to increase capacity for surveillance of adverse effects of both medical and non-medical exposures.

Population-based cancer registries

Historic developments

Population-based registries were introduced at state and territory level in Australia in the 1970s and were extended progressively to achieve national coverage [18]. Australia has had published cancer registry data for the total population since 1982 by combining data from cancer registries across Australia's eight states and territories [18]. Data items accord with recommendations of the International Agency for Research on Cancer and the International Association of Cancer Registries [18]. These data are included in volumes of Cancer Incidence in Five Continents by age, sex, primary anatomic site, and morphology [19]. Australian data are compiled nationally by the Australian Institute of Health and Welfare (AIHW), including all invasive cancers apart from squamous and basal carcinomas of the skin. In-situ cancers are also recorded in some jurisdictions for selected primary sites (e.g., bladder, skin (melanoma),and breast) [18]. The AIHW releases cancer incidence, mortality and survival data annually by primary site which are made available by calendar year, age, sex, place of residence (e.g., by geographic remoteness and area SES), and periodically by Aboriginal status and country of birth [18]. These data enable monitoring of cancer incidence, mortality and survival by cancer primary site and morphology, stratified socio-demographically and by calendar year.

Environmental studies

Australian cancer registry data have been used to assess cancer risks from: (a) uranium mining;[13] (b) aircraft maintenance work; [14] (c) atomic testing; [16] (d) asbestos mining; [20] (e) employment in asbestos-related construction and insulation; [16] employment in the petroleum industry; [17] (f) sun exposure; [21] (g) military service; [16] (h) exposure to toxic waste; [16] (i) farming; [16] and (j) a wide range of other occupational exposure [16]. Associated investigations have varied in design from cross-sectional to historic cohort, often with nested case-control sub-studies.

Linked population-based cancer registries and medical exposures

Population registries have served many purposes. In Australia, they enable routine surveillance of cancer incidence, mortality and survival, including evaluation of cancer screening, HPV vaccination, and cancer-treatment pathways [22]. While cancer registries have significant standalone value, linking data from them with population-based hospital and universal health insurance data has a multiplier effect [23]. In jurisdictions where this linkage is most advanced, a more powerful monitoring of all-of-population and all-of-health system services and outcomes has become possible along the treatment pathway [24]. These data have been used to identify gaps in service delivery for remedial action [23, 24]. The linked data cover all cancers other than non-melanoma skin cancers, describing their anatomic stage at diagnosis (solid tumours), accompanying comorbidity, time to treatment start, treatment practices, side-effects of care in the short and late term, and survival (all causes and cancer-specific). [23]. The data enable assessment of service delivery in the context of clinical guidelines and optimal care pathways. Emerging initiatives include complementing data linkage with sociodemographic data from the Australian Bureau of Statistics [7]. This and other linkage of cancer data from the Australian Institute of Health and Welfare are used to produce de-identified linked data, accessed remotely in secure laboratory settings, and with independent curation of outputs for privacy protection [25]. There are many administrative and research applications of these data, among them assessing long-term toxicity from novel treatments, including new and expensive targeted therapies.

Historic developments in monitoring clinical services, outcomes and side-effects

Data linkage between cancer registries, screening, medical diagnostics and treatment-procedure databases has occurred periodically in Australia since the 1980s, with marked increases in intensity in the 1990s to monitor cancer screening [22]. Registries have been used actively to assess effects of screening on cancer incidence, stage at diagnosis, grade, mortality and survival [26, 27]. Screening outcome indicators have included cancer size, stage and grade at diagnosis, and frequency of interval cancers occurring between cycles of screening. This data linkage framework was further extended with the introduction of bowel screening in 2006 [28]. Case-control study designs were used to investigate effects of screening on prevention, as for invasive cancer of the cervix [29]. Potential for overdiagnosis has been investigated [26].

Data linkage facilities were established across Australia, commencing in the 1990s with introduction of the Western Australian Data Linkage System, which incorporated standard processes of de-identification to protect privacy. De-identified linked data have been housed in external laboratory settings for remote access by researcher analysts and with curation of outputs to ensure compliance with ethics approved protocols and other established means of privacy protection (e.g., separation of patient identifiers and clinical content data) [22, 23, 25].

Present status of linked registry-administrative data

Jurisdictional registries are at differing levels of development along the data linkage pathway advocated in Australia [22]. Data linkage is most extensive in the largest jurisdiction of NSW (where about a third of residents reside), where the following data are linked into a jurisdiction-wide master linked dataset:

- NSW Cancer Registry (population-based) – enables ascertainment of cancer incidence, mortality, and survival data by cancer characteristics (primary site, morphology and degree of spread) and socio-demographic characteristics (age at diagnosis, sex, area SES, residential remoteness, and residence by local health district and primary health network), Aboriginal and Torres Strait Islander status, culturally and linguistically diverse (CALD) status, and calendar year period.

- NSW Clinical Cancer Registry data – enable collection of additional clinical variables for selected NSW public hospitals [4].

- NSW hospital inpatient data (population-based) – enable ascertainment of linked hospital-based data on diagnostic and treatment procedures, plus data on other non-cancer health conditions and comorbidities recorded in hospital patients.

- Radiotherapy centre data (population-based) – enable ascertainment of radiotherapy data on treatments, target sites, fractions, and doses.

- Medical Benefits (population-based) – enables inclusion of extracts of universal health insurance claims for private health care, including care provided in ambulatory settings by general practitioners and specialists.

- Pharmaceutical Benefits (population-based) – enables inclusion of universal health insurance claims for pharmaceutic expenses, including for services provided through general practitioners and specialists.

- MADIP data (population-based) - enable use of extracts of population census, welfare, and employment data for analysis of social determinants of disease.

- NSW-based screening data (population-based) – enable addition of breast-screening and historic cervix screening cytology data.

- National death records (population-based) – enable population-wide ascertainment of dates and causes of death.

- Other planned linkages – these include the NSW component of contemporary cervical and bowel screening data, HPV vaccination data, and nationwide international departure records.

Applications of linked data for identifying clinical side effects

Adverse effects of cancer care can range from surgery- related complications to damage to healthy tissues from high-intensity radiation therapy and medications [30]. Although toxicity studies are used premarketing of new medications, plus human trials, this testing can miss clinical side effects that emerge many years, even decades, after release [31]. Other side-effects could be missed because they are infrequent.

Common late effects of cancer therapy may include increased risk of other cancers from chemotherapy, hormone therapy or radiotherapy [32]. Examples include increases in radiogenic leukemias and breast, lung, thyroid, bone and gastrointestinal cancers (e.g., cancers of the stomach, liver, large bowel, and pancreas) [32]. Chemotherapy induced leukemias can result from treatments by alkylating agents, platinum-based drugs, and anthracycline and platinum-based drugs [32]. These can often be detected by cancer registries in multiple- primary studies, without linkage. Non-cancer health effects detectable through data linkage can include cardiac and other vascular diseases, reduced pulmonary, renal and liver function, and a range of other conditions such as infertility, osteoporosis, reduced sensory perception, thyroid conditions, reduced memory and cognition, and neuropathy [30, 31].

Of particular interest is the emergence of novel immunotherapies and targeted therapies, which are already demonstrating significant gains, as for example for lung, thyroid, colorectal and haematological malignancies [10, 33]. The introduction of novel therapies may be too early for adverse effects in the longer term to be fully documented. This is an important research frontier requiring active surveillance and investigation such that results can inform trade-off decisions on choice of preferred therapies. Surveillance of long-term outcomes with established databases could be of great benefit and should be given a high priority.

Summary and conclusions

Population-based cancer registries have been operational in Australia since the 1970s with principal roles including monitoring invasive cancer incidence, mortality and survival by cancer type for the population overall and sub-groups classified by age, sex, residential remoteness, socioeconomic status, country of birth and Indigenous status.

This monitoring has been extended to show treatment timelines and care patterns through data linkage and access of analysts to de-identified data. Interpretation is improved by the increased availability of linked data on stage and other prognostic indicators across sociodemographic predictors. Social determinants of cancer, prognostic, treatment and survival indicators can be included using linked census, social welfare and employment data.

Population-based cancer registries are continuing with their traditional cancer surveillance roles and monitoring of treatment patterns across the population, while placing increased emphasis on accompanying comorbidities and patient reported experiences and outcomes. Molecular research has led to more targeted immunotherapies and other therapies, with trials providing evidence of marked improvements in case outcomes.

An emerging focus is the use of linked data networks to better identify and monitor treatment side effects, including late effects such as heart and other organ damage. The long-term benefits and harms of these therapies require better definition, including in older ages where multi-comorbidities apply. We propose to further test the utility of population-wide linked data networks to support service planning, monitoring and evaluation, and population health and health-services research.

Clinical cancer registries ideally would be added to these linked data systems to provide selective drill-down value adding, improve the quality of data, and collect additional data for clinical research.

References

References

1. Australian Institute of Health and Welfare. Data linkage: accessing data. *Available at: https://www.aihw.gov.au/our-services/data-linkage [Accessed: 1 October 2021].*
2. Cancer Institute New South Wales. Request linked unit record data for research. *Available at: https://www.cancer.nsw.gov.au/research-and-data/cancer-data-and-statistics/request-linked-unit-record-data-for-research [Accessed: 1 October 2021].*
3. Cancer Institute New South Wales. Reporting for better cancer outcomes program. *Available at: https://www.cancer.nsw.gov.au/what-we-do/supporting-cancer-care/reporting-for-better-cancer-outcomes-program [Accessed: 1 October 2021].*
4. Australian Institute of Health and Welfare. Clinical quality registries. *Available at: https://www.aihw.gov.au/reports/australias-health/clinical-quality-registries [Accessed: 1 October 2021].*
5. Li Ming, Roder David, D’Onise Katina, Walters David, Farshid Gelareh, Buckley Elizabeth,

Karapetis Christos, Joshi Rohit, Price Timothy, Townsend Amanda, Miller Caroline, Currow David, Powell Kate, Buranyi-Trevarton Dianne, Olver Ian. Female breast cancer treatment and survival in South Australia: Results from linked health data. *European Journal of Cancer Care.* 2021; 30(5)DOI

6. Buckley Elizabeth, Elder Elisabeth, McGill Sarah, Kargar Zahra Shahabi, Li Ming, Roder David, Currow David. Breast cancer treatment and survival differences in women in remote and socioeconomically disadvantaged areas, as demonstrated by linked data from New South Wales (NSW), Australia. *Breast Cancer Research and Treatment.* 2021; 188(2)DOI
7. Australian Bureau of Statistics. Multi-Agency Data Integration Project (MADIP). *Available at: https://www.abs.gov.au/about/data-services/data-integration/integrated-data/multi-agency-data-integration-project-madip [Accessed: 3 October 2021].*
8. Mathews John D., Forsythe Anna V., Brady Zoe, Butler Martin W., Goergen Stacy K., Byrnes Graham B., Giles Graham G., Wallace Anthony B., Anderson Philip R., Guiver Tenniel A., McGale Paul, Cain Timothy M., Dowty James G., Bickerstaffe Adrian C., Darby Sarah C.. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ (Clinical research ed.).* 2013; 346DOI
9. Dokmanovic Milos, Wu Wen Jin. Monitoring Trastuzumab Resistance and Cardiotoxicity: A Tale of Personalized Medicine. *Advances in Clinical Chemistry.* 2015; 70DOI
10. Falzone Luca, Salomone Salvatore, Libra Massimo. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. *Frontiers in Pharmacology.* 2018; 9DOI
11. Australian Government, Therapeutic Goods Administration. Australian Advisory Committee on Medicines (ACM). *Available at: https://www.tga.gov.au/committee/advisory-committee-medicines-acm [Accessed: 4 October 2021].*
12. Comba P, Fazzo L, Fusco M, Benedetti M, Pirastu R, Ricci P. The contribution of cancer registries in environmental health studies. *Epidemiol Prev.* 2011; 35(5-6, Suppl 4):189-191. Available from: https://europepmc.org/article/med/22166301. [Accessed: 3 October 2021].
13. Woodward A., Roder D., McMichael A. J., Crouch P., Mylvaganam A.. Radon daughter exposures at the Radium Hill uranium mine and lung cancer rates among former workers, 1952-87. *Cancer causes & control: CCC.* 1991; 2(4)DOI
14. D'Este Catherine, Attia John R., Brown Anthony M., Gibson Richard, Gibberd Robert, Tavener Meredith, Guest Maya, Horsley Keith, Harrex Warren, Ross James. Cancer incidence and mortality in aircraft maintenance workers. *American Journal of Industrial Medicine.* 2008; 51(1)DOI
15. Iqubal Ashif, Iqubal Mohammad Kashif, Sharma Sumit, Ansari Mohd Asif, Najmi Abul Kalam, Ali Syed Mansoor, Ali Javed, Haque Syed Ehtaishamul. Molecular mechanism involved in cyclophosphamide-induced cardiotoxicity: Old drug with a new vision. *Life Sciences.* 2019; 218DOI
16. South Australian Cancer Registry. Epidemiology of cancer in South Australia. *Adelaide: Department of Human Services; 2000.*
17. Gun R, Pilotto L, Ryan P, Griffith E, Pratt N, Ewing S, Dimitri H, Phillips S, McDermott B. Health Watch: The Australian Institute of Petroleum Health Surveillance Program. Eleventh Report. Adelaide: The University of Adelaide Dept Public Health. *Available at: https://www.aip.com.au/programs/health-watch [Accessed: 4 October 2021].* 2000.
18. Australian Institute of Health and Welfare. About Australian Cancer Database. *Available at: https://www.aihw.gov.au/about-our-data/our-data-collections/australian-cancer-database/about-australian-cancer-database [Accessed: 1 October 2021].*
19. Bray F, Colombet M, Mery L, Pineros M, Znaor A, Zanetti R, Ferlay J. Cancer incidence in five continents. Volume XI. IARC Scientific Publication No. 166. Lyon: IARC; 2021.
20. Berry G., Reid A., Aboagye-Sarfo P., Klerk N. H., Olsen N. J., Merler E., Franklin P., Musk A. W.. Malignant mesotheliomas in former miners and millers of crocidolite at Wittenoom (Western Australia) after more than 50 years follow-up. *British Journal of Cancer.* 2012; 106(5)DOI
21. Elwood J. Mark, Jopson Janet. Melanoma and sun exposure: An overview of published studies. *International Journal of Cancer.* 1997; 73(2)DOI

22. Cancer Australia. A national cancer data strategy for Australia. Canberra: Commonwealth Government; 2008.
23. Lawrence Glenda, Dinh Isa, Taylor Lee. The Centre for Health Record Linkage: A New Resource for Health Services Research and Evaluation. *Health Information Management: Journal of the Health Information Management Association of Australia.* 2008; 37(2)DOI
24. Olver Ian N.. Linking data to improve health outcomes. *The Medical Journal of Australia.* 2014; 200(7)DOI
25. SAX Institute. SURE: Secured Unified Research Environment. Introduction to SURE. *Available at: https://www.saxinstitute.org.au/our-work/sure/ [Accessed: 3 October 2021].*
26. World Health Organization, European Regional Office. Screening programmes: a short guide. Increase effectiveness, maximize benefits, and minimize harms. Denmark: WHO, 2020. *Available at: https://apps.who.int/iris/bitstream/handle/10665/330829/9789289054782-eng.pdf [Accessed: 4 October 2021].*
27. Morrell Stephen, Taylor Richard, Roder David, Robson Bridget, Gregory Marli, Craig Kirsty. Mammography service screening and breast cancer mortality in New Zealand: a National Cohort Study 1999-2011. *British Journal of Cancer.* 2017; 116(6)DOI
28. Parkin Cameron J., Bell Stephen W., Mirbagheri Naseem. Colorectal cancer screening in Australia: An update. *Australian Journal of General Practice.* 2018; 47(12)DOI
29. Yang Baohui, Morrell Stephen, Zuo Yeqin, Roder David, Tracey Elizabeth, Jelfs Paul. A case-control study of the protective benefit of cervical screening against invasive cervical cancer in NSW women. *Cancer causes & control: CCC.* 2008; 19(6)DOI
30. National Cancer Institute, USA Government. Side effects of cancer treatment. Side effects of cancer treatment. *Available at: https://www.cancer.gov/about-cancer/treatment/side-effects [Accessed: 7 October 2021].*
31. National Cancer Institute, USA Government. Side effects of cancer treatment. Late effects of cancer treatment. *Available at: https://www.cancer.gov/about-cancer/coping/survivorship/late-effects [Accessed 7 October 2021].*
32. American Cancer Society. Second cancers related to treatment. *Available at: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/second-cancers-in-adults/treatment-risks.html [Accessed 7 October 2021].*
33. Offidani M, Corvatta L, More S, Olivieri A. Novel experimental drugs for treatment of multiple myeloma. *J Experimental Pharmacology.* 2021; 13:368-369. DOI